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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/664,326	09/18/2000	Paul Habermann	02481.1693	4393

22852 7590 01/07/2003

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20006

EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	13

DATE MAILED: 01/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/664,326	Applicant(s) HABERMANN ET AL.	
	Examin r Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

Claims 1-14 are pending. Claims 1-5 and 10-14 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 6-9 have been considered in this Office Action.

Drawing

The drawing filed September 18, 2000 has been approved by the draftsperson.

Objections Withdrawn

Specification

The objection to the Specification for lacking a Brief Description of the Drawing is withdrawn in light of the amendment.

Rejections Withdrawn

The rejection of Claims 8 and 9 under 35 U.S.C. 112, second paragraph as unclear as to the meaning of "expression" is withdrawn in light of the amendment to Claim 8.

The rejection of Claim 6 under 35 U.S.C. 112, second paragraph as unclear as to the nexus of the expression rate and the activity of the protein in the culture supernatant is withdrawn in light of the amendment and arguments.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Rejection: Claims 6 and 7 are unclear as to what is considered a "suitable" signal peptide (in step (d) of Claim 6 and last line of Claim 7). For example, is a signal peptide "suitable" if any level of protein activity is found in the culture supernatant in step (b)? Or, is a "suitable" signal peptide one that results in greater (or lesser) protein activity in the culture supernatant greater than a particular control (e.g. a hirudin derivative without a signal peptide) or is it the signal peptide that provides the highest activity in step (b))? Claims 8 and 9 are also rejected since they depend from these indefinite claims and do not correct the deficiencies.

Response to Arguments: Applicants argue that whether a signal peptide is "suitable" depends on the application. Applicants define "suitable" as "appropriate to a given purpose or occasion" and further argue that the primary purpose of the requirement of definiteness of claim language is to ensure the scope of the claim is clear so that the public is informed of the boundaries of what constitutes infringement and that the ordinary meaning of the term "suitable" clearly defines the boundaries. This argument is not persuasive because in the present case the "purpose or occasion"

has not been defined. A claim may be rendered indefinite by reference to an object that is variable (MPEP 2173.05(b). In the present case, the variable object is the "suitable" signal peptide because there are an unlimited number of "purposes or occasions" that would lead to "suitable" signal peptides of various identities. Moreover, the signal peptides considered "suitable" for even a single purpose would vary from person to person. For example, one might consider only the signal peptide that results in the highest hirudin activity as "suitable" while another person testing the same group of signal peptides may consider the signal peptides having the top four highest hirudin activity as "suitable for the same purpose. Thus, the metes and bounds of the claim are unclear and the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for selecting a suitable signal peptide for secretory expression of hirudin or a hirudin derivative using the method steps of the claims, does not reasonably provide enablement for a process for selecting a suitable signal peptide for secretory expression of any desired protein using the method steps of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

It appears that undue experimentation would be required to determine whether a signal peptide selected as suitable for hirudin expression would be suitable for expression of other "desired proteins". Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The rejection given in the previous Office Action is given below followed by a response to Applicants arguments.

Rejection:

Breadth of Claims: The Claims are drawn to methods of selecting a suitable signal peptide for secretory expression of any desired protein by expression of hirudin connected to various signal peptides and comparing the expression rates, represented by the hirudin antithrombotic activity in the culture supernatant, as an indicator of the suitability of the signal peptide.

Nature of the Invention: The nature of the invention requires that the results of finding a suitable signal peptide for hirudin would be predictive of the suitability of that signal peptide for any other desired protein.

Amount of direction/guidance and presence/absence of working examples: The present Specification describes a method of finding signal peptides for expression of

hirudin. There are no examples of using a fusion of hirudin to various signal peptides to find a suitable signal peptide for any other proteins.

State of the Prior art, Relative Skill of those in the art, and Predictability/Unpredictability of the art: It appears that those of relative skill in the art and the state of the prior art recognize an inability to predict the secretion efficacy of a given signal sequence for a given peptide as evidenced by Wong et al. (U.S. Patent No. 5,652,139, 1997). Wong et al. report that in trying to find a suitable signal peptide for IGF-1 expression in E. coli, several signal sequences reported to effectively secrete E. coli and/or heterologous proteins were found to be unable to secrete mature IGF-1 (see Col. 5, lines 6-16). Thus, it appears that whether or not a signal peptide, determined to be "suitable" by the method of the present invention, would be suitable for desired proteins other than hirudin would be highly unpredictable.

Quantity of Experimentation: For the reasons described above, practicing the claimed method to determine the suitability of a signal peptide for secretory expression of desired proteins other than hirudin would require undue experimentation.

Amendment of Claim 6 substituting "hirudin" for "a desired protein" in lines 1-2 (incorporation of the limitations of Claim 9 into the independent claim) would overcome this rejection.

Response:

Applicants appear to argue that the signal peptide found suitable for use with hirudin in the claimed method "should for the most part be" independent of the peptide attached to it and that the method of the invention provides a strong indication of

whether or not a signal peptide has general applicability. This argument has been considered but is not deemed persuasive because the evidence (Wong et al.) shows that those of skill in the art recognize the inability to predict the secretion efficacy of a given signal sequence for a given peptide (see Wong et al. U.S. Patent No. 5,652,139, 1997; especially Col. 5, lines 6-16). Wong et al. state that there are "prior reports of inabilities to predict the secretion efficacy of a given signal sequence for a given peptide" (Wong et al. Col. 5, lines 14-16). Thus, absent evidence that the claimed method indicates whether or not a signal peptide has general applicability, the rejection is maintained.

Applicants argue that experiments "could be easily performed to determine whether other proteins are secreted" (emphasis added, p. 6, lines 14-16 of Response filed Oct. 15, 2002 (Paper No. 12)). However, this is not adequate guidance as to the nature of the proteins for which the signal peptide could be "suitable", but is merely an invitation to the artisan to use the disclosed method as a starting point for further experimentation to determine whether the signal peptides could be used successfully with proteins other than hirudin.

Thus, for the reasons stated above and in the previous Office Action, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Achstetter et al. (Gene (1992) 110: 25-31) in view of Schmid et al. EP 0 448 093 (1990; cited in IDS of Paper No. 4).

The reasons for the rejection provided in the prior Office Action are repeated below followed by a response to Applicants arguments.

Rejection:

The examiner notes that U.S. Patent No. 5,919,895 ('895 patent) has been used as the English language equivalent of EP 0 448 093. Therefore, references to Schmid et al. will refer to the '895 patent.

Achstetter et al. disclose a method of selecting a signal peptide for secretory expression of hirudin or a hirudin derivative (p. 26, Col. 1, lines 27-30) comprising (a) expressing in a culture medium, hirudin having antithrombotic activity, and which has a defined amino acid, aa_x, at its N terminus, wherein said amino acid aa_x, is connected via

its N-terminal to a signal peptide to be tested; (b) determining the expression rate by measuring protein activity in the culture supernatant; (c) repeating steps (a) and (b) with various signal peptides; and (d) selecting the suitable signal peptide by comparing the expression rates represented by the hirudin antithrombotic activity found in step (b). It is noted that Claim 6 does not provide any reference sequence to determine whether the "defined amino acid, aa_x" is an extra amino acid in addition to the 65 or 66 amino acids of the native hirudin sequence or if it is just the N-terminal amino acid of hirudin. Native hirudin contains either 65 or 66 amino acids and a hirudin derivative could contain any number of amino acids. Therefore, the limitation "which has a defined amino acid, aa_x, at its N-terminus, wherein said amino acid, aa_x is connected via its N-terminal to a signal peptide" is considered to encompass any signal peptide-hirudin protein wherein the signal peptide is at the N-terminus. Thus, the hirudin protein described in the method of Achstetter et al. is considered to have a defined amino acid, aa_x, at its N-terminus, wherein said amino acid aa_x is connected via its N-terminal to a signal peptide to be tested.

Achstetter et al. teach that the selection method involves expression in yeast and do not teach that the method involves expression in *E. coli*.

Schmid et al. teach that the expression of hirudin in *E. coli* would be advantageous over processes known in the art using yeast because "the cultivation of yeast cells takes longer and is more demanding than that of bacteria, for example, E. coli (Col. 2, lines 15-16). The bacteria, *E. coli*, appears to be preferred because of the availability of *E. coli* strains which show massive protein secretion into the culture

medium (Col. 3, lines 32-34). Schmid et al. disclose a method of expressing Ala-hirudin derivatives in *E. coli* (Col. 6, lines 1-11) and suggest hirudin derivatives having any one of the amino acids Leu, Ile, Ala, Val, Gly, Ser, Asp, Glu, Asn, Gln, His, Met, Phe, and Tyr at the N-terminus wherein the amino acid is connected via its N-terminal to a signal peptide (Col. 2, lines 51-67). Schmid et al. state it is possible to obtain 2 g/L of a hirudin derivative with the N-terminal sequence of SEQ ID NO :1 (Ala-hirudin) in the culture supernatant of an E. coli secretor (Col. 3, lines 32-35).

Therefore, it would be obvious to one of ordinary skill in the art at the time of the invention, to practice the method of selecting signal peptides for the secretory expression of hirudin described in Achstetter et al. in E. coli using a aa_x-hirudin sequence as disclosed in Schmid et al. One of ordinary skill in the art would have been motivated to use E. coli in the method of selecting signal peptides because Schmid et al. state that the cultivation of yeast cells takes much longer and is more demanding than bacteria. Moreover, Schmid et al. shows that the method disclosed therein is highly successful in producing high concentrations of active Ala-hirudin (see Col. 3, lines 24-26). Thus, it appears that the claims are unpatentable over Achstetter et al. in view of Schmid et al. for the reasons cited above.

Response to Arguments:

Applicants argue that the examiner has not considered the Schmid et al. reference as a whole and that Schmid et al. describe disadvantages of expression in E. coli including low yield. This argument has been considered but is not deemed persuasive for the following reasons. Schmid et al. describes the disadvantages of both

yeast and E. coli expression systems, however, the Schmid et al. patent is focused on improving the E. coli expression system to result in high yields of hirudin (see Col. 2, lines 23-27). It appears that Schmid et al. achieve this goal since they obtain 2 g/L of a hirudin derivative in the culture supernatant of an E. coli secretor (Col. 3, lines 32-35). Since the goal of both Schmid et al. and Achstetter et al. is to increase production of hirudin it would have been obvious to one of ordinary skill in the art at the time of the invention, to practice the method of selecting signal peptides for the secretory expression of hirudin described in Achstetter et al. in E. coli using a aa_x-hirudin sequence as disclosed in Schmid et al. One of skill in the art, with both the Achstetter et al. and Schmid et al. references in hand, would have been motivated to use E. coli in the method of selecting signal peptides because the skilled artisan would have recognized that the cultivation of yeast cells takes much longer and is more demanding than bacteria and because Schmid et al. shows that the method disclosed therein is highly successful in producing high concentrations of active Ala-hirudin (see Col. 3, lines 24-26). Thus, the rejection is maintained.

Applicants argue that there is no motivation to use the yeast signal peptides of Achstetter et al. in the Schmid et al. system which is optimized for E. coli signal peptides. This argument is not persuasive because the claims are not limited to the type of signal peptides that are used in the method. In fact, the claimed method is used to find signal peptides that are "suitable" for undefined purposes. Therefore, the rejection is maintained.

Conclusions

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application contains claims 1-5 and 10-14 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
December 31, 2002

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600